



Research paper

Halloysite-based hybrid bionanocomposite hydrogels as potential drug delivery systems



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ARTICLE INFO

Dedicated to the memory of Professor Ali Akbar Entezami who passed away in the summer of 2015.

Keywords:

Oxidized starch

Chitosan

Halloysite

Drug delivery systems

ABSTRACT

In this investigation, the preparation of novel Halloysite-based chitosan/oxidized starch (Hal/CTS/OSR) Hybrid bionanocomposite hydrogels is described. The obtained hybrid hydrogels were characterized by using FT-IR, SEM, XRD, TGA and DTG techniques. In addition, the efficiency of hydrogels as drug delivery systems was studied. The results demonstrated that depending on experimental parameters, such as the ratio of CTS/OSR, and the type of Hal nanotubes (modified or unmodified), the hydrogel properties can be affected and modulated significantly. 74.3%, 71.2% and 69.45% MTZ release were observed for CTS/OSR/mHal 10, CTS/OSR and CTS/OSR/Hal 10 respectively.

1. Introduction

In life science, considerable efforts have been devoted to both natural and synthetic hydrogels due to their excellent properties that make them suitable for a wide range of applications, including drug delivery system (Kim et al., 2014), pharmaceutical and medical (Peppas et al., 2000; Arion, 2001; Browning et al., 2012), tissue engineering (Lee and Mooney, 2001; Van Vlierberghe et al., 2011), food industry (Farris et al., 2009), environmental science (Crini and Badot, 2008). Hydrogels are defined as three-dimensional hydrophilic polymeric networks that can absorb and hold amounts of water, physiological solution, or saline but do not dissolve because of their crosslinked structures (Satarkar et al., 2010; Ahmed, 2015). Polysaccharides as natural materials, currently is receiving enormous attention in the preparation of the biocompatible hydrogels (Vieira et al., 2008; Thakur and Thakur, 2014). Among these natural materials, chitosan (CTS) and starch has a widespread application as hydrogels scaffolds.

Starch and its derivatives have been confirmed to be interesting biopolymers due to their biodegradability, renewability and easy availability (Hoover, 2001; Averous, 2004). Amylopectin and amylose are two types of glucose units which could be found in starch structures (Li et al., 2014). Moreover, chemically modification of starch can be increased its industrial applications. For example, the oxidation of starch, especially its periodate-mediated oxidation that causes the cleavages of C₂–C₃ bonds in order to form dialdehydes has been reported previously

(Fig. 1A) (Jackson and Hudson, 1937; Guthrie, 1962; Mehlretter, 1966; Zhang et al., 2007). Thus, oxidized starch can easily form imine linkage with chitosan or with other compounds bearing amine groups via Schiff base chemistry (Tang et al., 2003).

As another important biopolymer, chitosan are known as the most abundant biopolymer in nature after cellulose which could be obtained by N-deacetylation of chitin (Fig. 1B). Chitosan not only has excellent antibacterial, antifungal and biodegradable properties but also has many reactive functional groups which make it modify easily (Anirudhan and Tharun, 2012; He et al., 2016). Although polysaccharide based hydrogels, especially chitosan, have many advantageous in drug delivery systems, the poor gel strength, stability and mechanical property of these hydrogels need to be further enhanced for practical applications (Liu et al., 2009a,b). To solve these problems, various strategies have been utilized such as mixing other polysaccharides with chitosan (Baran et al., 2004; Vieira et al., 2008), using cross-linking agents (Welsh et al., 2002; Schiffman and Schauer, 2007) and incorporation of inorganic nanofillers (Kabiri et al., 2009; Zheng and Wang, 2009; Mittal et al., 2014; Fahim et al., 2015). Among them, the inclusion of nanofiller into bio-based materials could be an effective and powerful solution to enhance these properties even at low concentration of nanofillers (Bordes et al., 2009). In this regard, in the past decades, clay nanofillers have attracted great attention from the medical industries and scientific communities because of their unique properties such as high surface area, drug encapsulation and absorption

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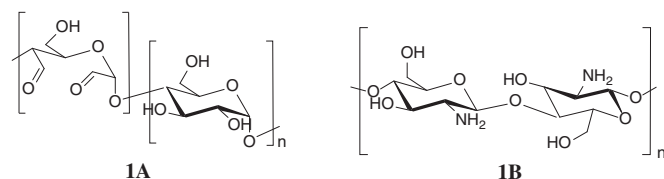


Fig. 1. Chemical structures of A) oxidized starch and B) chitosan.

capabilities (Bitinis et al., 2011; Lai et al., 2013; Zhou et al., 2014).

Halloysite nanotubes (Hal), as a kaolinite mineral, consists of fibrous crystals or myriad thin tubular with the chemical composition $\text{Al}_2(\text{OH})_4\text{Si}_2\text{O}_5(2\text{-H}_2\text{O})$ (Soheilmoghaddam and Wahit, 2013; Yuan et al., 2015; Zhang et al., 2016). Hal nanotubes are 0.5–1.5 μm in length with an inner diameter of 10–30 nm and an outer diameter of 50–70 nm (Liu et al., 2012). Compared to other nanofillers, Hal nanotubes have some advantageous such as biocompatibility (Cavallaro et al., 2015), low cost, hydrophilic properties and capability to encapsulate drugs (Massaro et al., 2015, 2016). With these unique properties, mHal can be loaded with guest molecules such as drugs and utilized for sustained release of chemical components (Wei et al., 2012; Lvov and Abdullayev, 2013; Tan et al., 2014; Hemmatpour et al., 2015). In recent years, a sizable number of researches have been focused on Hal reinforced biopolymers. For example, Hal being embedded within chitosan/Poly (acrylic acid) hydrogels and enhanced the adsorption of ammonium from aqueous media (Zheng and Wang, 2009). In another report, Hal was used as a nanofiller to tune the thermal, swelling, drug loading and in vitro drug release characteristics of the kappa-carrageenan hydrogel (Sharifzadeh et al., 2016). In one work, mHal was used as nanofiller in order to fabricate Halloysite/potato starch films (He et al., 2012). Furthermore, the positively (inner) and negatively (outer) charged surface of Hal nanotubes enhance the loading and absorption ability of charged molecules or drugs via electrostatic interactions (Lvov et al., 2008). However, like other nanofillers, dispersion of Hal into hydrogel and polymer matrix is an important issue which limited the application of Hal in the bio-based hydrogel fabrications (Lvov et al., 2008; Cavallaro et al., 2013). Functionalization of Hal with different types of silane coupling agents has been utilized as an easy way to enhance Hal dispersal in a polymer backbone. In this method, silanes were grafted onto the surface of Hal nanotubes via condensation with the surface hydroxyl groups (Krishnaiah et al., 2017). Inspired by the considerations presented above, incorporation of unmodified or modified Hal (mHal) into the bio-based hydrogels appears indeed attractive.

Articles survey demonstrated that the incorporation of Hal nanoparticles into the oxidized starch hydrogel networks has not been explored previously. Moreover, the effect of Hal nanotubes on the properties of CTS/OSR hydrogels such as swelling equilibria, thermal stability and drug release capacity has also remained undiscovered. The aim of this investigation is to prepare novel chitosan-crosslinked oxidized starch bio-nanocomposite hydrogels with modified or unmodified Hal. Obtained hybrid hydrogels were characterized using FT-IR, SEM, XRD, TGA and DTG. The effect of modified and unmodified Hal nanoparticles and the ratio of CTS/OSR on swelling and release profile of metronidazole (MTZ) as a model drug were investigated.

2. Materials and methods

2.1. Materials

A medium molecular weight chitosan with 200–800 cP viscosity (1 wt% of chitosan in 1 wt% of acetic acid solution), Sodium tripolyphosphate (STPP, technical grade 85%) and Halloysite supplied from Sigma-Aldrich Co., USA. Corn oxidized-starch (with Max 12 wt% humidity) purchased from Glokozan Co. (Gazvin, Iran). Aminopropyltriethoxysilane (APTES) was obtained from Acros.

Metronidazole (MTZ) was kindly donated from Shahid Ghazi Pharmaceutical (Tabriz, Iran). All other chemicals were analytical grade and used as received. Distilled water was used throughout this study.

2.2. Preparation of chitosan/oxidized-starch hydrogel beads

In order to optimize the best ratio of OSR/CTS without Halloysite nanofiller, some experiments were carried out. In a typical procedure, 1 g of chitosan was added to 35 ml distilled water followed by addition of 2.5 ml acetic acid. The mixture stirred until a clear homogeneous viscous solution obtained. Oxidized starch solutions of different weights (1, 2, 4 and 8 g) were prepared in distilled water at room temperature. Two solutions were mixed together and stirred at 90 °C. After cooling the mixture reaction to room temperature, the suspensions were injected dropwise using 10 ml sterile syringe (2 mm diameter) into 400 ml aqueous solution containing 4 g of STPP and stirred slowly for 30 min. Thereafter, the obtained beads were kept in solution for 24 h in order to complete crosslinking process. The produced beads were collected from solution and washed with fresh distilled water for six times followed by drying in an oven at 40 °C for overnight. According to the experiments, the best ratio of OSR/CTS was found to be 2/1.

2.3. Modification of Hal nanotubes

Hal nanotubes were modified according to the previous reported literature (Krishnaiah et al., 2017). Typically, into a 500 ml round bottom flask equipped with a magnetic stirrer containing 250 ml ethanol (95%) and 0.5 ml of acetic acid, 6 g of silane coupling agent i.e. APTES was added and allowed to stir vigorously at 60 °C for 15 min. Then 25 g of Hal nanotubes were added to the solution and stirred at 60 °C for 2 h. Finally, the product was filtered and washed with ethanol and dried at room temperature for 24 h and then dried under vacuum at 100 °C for 8 h to remove the moisture and solvent.

2.4. Preparation of Halloysite-based chitosan/oxidized-starch nanocomposite hydrogel

With optimum condition in hand (2/1 ratio of OSR/CTS) and the modification of Hal according to the procedure described by Manickam et al. For the first time, a novel Halloysite-based CTS/OSR nanocomposite hydrogel beads (Hal/CTS/OSR) were prepared, using sodium tripolyphosphate (STPP) and Hal or mHal as the co-cross-linking agent and nanofiller respectively. Scheme 1 illustrates the general procedure for the preparation of bionanocomposite hydrogel beads. These nanocomposite hydrogel beads (Hal/CTS/OSR) were synthesized with the same procedure which mentioned in the previous section. In this protocol, desired amount of Hal or mHal was added to 10 ml distilled water and dispersed ultrasonically at room temperature for 30 min. Then, 2 g oxidized-starch was added to this suspension followed by addition of chitosan solution (1 g of chitosan in 35 ml distilled water with 2.5 ml acetic acid). Thereafter, the reaction mixture was stirred vigorously at 90 °C for 6 h. Finally, nanocomposite hydrogel beads were formed according to the procedure that explained for the preparation of CTS/OSR hydrogel beads. The pure and nanocomposite hydrogels were assigned as CTS/OSR, CTS/OSR/mHal10 and CTS/OSR/Hal10 respectively, where x = 10 exhibiting Hal wt% and m was denoted as modified Hal nanotubes, in the structure of Hydrogels.

2.5. Instrumentation

Fourier transform infrared (FT-IR) spectrum of the synthesized compounds was collected with a Tensor-27 Bruker FT-IR spectrometer on a KBr disk over the range of 500–3500 cm^{-1} . TGA of samples was carried out on the dried samples with a heating rate of 10 °C/min (from 20 to 800 °C), using a Linseis L81A1750 (Germany) under high-purity

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